Testimony
Before the Committee on Government Reform
United States House of Representatives

The NIH Biomedical Research Response to Influenza

Statement of

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For Release on Delivery
Expected at 1:00PM
Wednesday, November 17, 2004

Mr. Chairman and Members of the Committee, thank you for the opportunity to discuss with you today the role of the National Institutes of Health (NIH) in helping to ensure that the nation has a reliable supply of safe and effective influenza vaccines.

Because the influenza viruses in circulation change somewhat from season to season, the U.S. supply of influenza vaccine must be renewed each year – and often contains flu viruses that are different from those used the previous year. The current technology for vaccine manufacture requires that key decisions, such as which viruses will be included and the number of doses needed, be made many months before the arrival of the influenza season. The serious vaccine shortage that has occurred this year underscores the difficulties we face in annually renewing the influenza vaccine supply, and highlights the pressing need to move toward adoption of a variety of vaccine manufacturing techniques that include newer technologies that may decrease the risk involved in vaccine production as well as improve flexibility and the speed at which the vaccines can be made.

The National Institute of Allergy and Infectious Diseases (NIAID), a component of NIH, is the lead agency for the conduct of research on all infectious diseases, including influenza. In that capacity, NIAID provides the scientific input required to facilitate the development of both new influenza vaccine technologies and novel antiviral drugs against influenza viruses.

Under this administration we have made tremendous progress. Immediately upon coming to HHS, Secretary Thompson, under the leadership of President Bush, began transforming the flu marketplace by investing in new technologies, securing more vaccines and medicines, and preparing stronger response plans. Total NIH funding for influenza research has grown more than three-fold in recent years, from $20.6 million in FY 2001 to a requested $65.9 million (320 percent) in the FY 2005 President's Budget. This is part of the largest investment ever made by the federal government in protecting against the flu.

NIAID Influenza Research

NIAID pursues an ambitious basic and applied research agenda on influenza, including viral biology, pathogenesis, host immune responses, and epidemiology, which underpin our many programs that are aimed at developing new and improved influenza countermeasures such as vaccines, therapies and diagnostic tools. Because influenza vaccines are the primary public health tools available to limit the disease burden caused by annual influenza epidemics, vaccine research has a very high priority. NIAID also supports several research activities specifically focused on identifying and countering any future influenza pandemic.

Basic Research

The development of new and effective influenza countermeasures rests on a foundation of basic research. Some basic research focuses on specific questions regarding the biology of the virus such as how it enters cells, replicates, mutates, evolves into new strains and induces an immune response, while other projects can be more broadly applied. For example, under a recent NIAID initiative called the Influenza Genome Project, NIAID will collaborate with researchers around the world to obtain the complete genetic sequence of several thousand human and animal influenza viruses. The resulting library of influenza sequences, some of which may be derived from samples collected decades ago, should add greatly to our understanding of what makes one strain more lethal than another, what genetic determinants most affect immunogenicity, and how the virus evolves over time. All of this is precisely the kind of information that will significantly enhance our ability to create more effective countermeasures.

Vaccines

Because influenza is such a highly transmissible virus, vaccines are essential tools for the control of influenza epidemics. The current system for the production of U.S. licensed influenza vaccines uses fertilized chicken eggs to grow influenza vaccine strains that have been selected to match the viruses likely to circulate in the coming influenza season. The viral particles are purified from the eggs, inactivated, and processed for distribution.

Although the egg-based technology has served us reasonably well for more than 40 years, there are several limitations to the current system that include: (1) a lengthy manufacturing process; (2) the need to forecast and select the virus strains to be used in the vaccine at least six months in advance of the influenza season; and (3) the annual need for hundreds of millions of fertilized chicken eggs to manufacture the vaccine. The decisions about which viral strains to include in the vaccine may not always be correct, but the long lead time required to acquire eggs for vaccine production makes mid-course corrective action virtually impossible. Additional limitations include the fact that some people are allergic to eggs and therefore cannot receive the classic vaccine. In addition, some influenza viruses do not grow well in chicken eggs and may in fact be virulent for the eggs, a circumstance that may result in delays bringing a vaccine to market and a possible decrease in the total number of doses available.

In each of the last two budgets, HHS has asked for $100 million to shift vaccine development from the cumbersome egg-based production to new cell-culture technologies, as well as to provide for year-round availability of eggs to provide for a secure supply and surge capacity. These new technologies will help produce flu vaccine more efficiently and provide more adaptability to unexpected problems or losses in production.

NIAID supports several research projects and other initiatives intended to foster the development of new influenza vaccines and manufacturing methods that are simpler, more reliable, yield more broadly cross-protective products, and provide more protection than those currently in use. For example, a technique developed by NIAID-supported scientists called reverse genetics allows scientists to manipulate the genomes of influenza viruses and to transfer genes between viral strains. The technique allows the rapid generation of seed viruses for vaccine candidates that exactly match the anticipated epidemic strain. By removing or modifying certain virulence genes, reverse genetics also can be used to convert highly pathogenic influenza viruses into vaccine candidates that are safer for vaccine manufacturers to handle.

To encourage participation by the pharmaceutical industry, NIAID supports Challenge Grants to fund the development of new influenza vaccine technologies. One approach under active development is the use of cell cultures to grow vaccine strains, rather than eggs. Another approach is to genetically engineer baculovirus, an insect virus not related to influenza, to express a gene that encodes an influenza coat protein such as hemagglutinin or neuraminidase. The engineered baculovirus is then grown in insect cell cultures, and the influenza protein that the virus produces is purified for use as a "recombinant subunit" influenza vaccine. A recent NIAID-supported Phase II clinical trial of a vaccine produced by Protein Sciences Corporation using this strategy showed that it is well tolerated and immunogenic; the company is conducting further

clinical evaluation of this product. Other new pathways for producing influenza vaccines include DNA-based approaches and the development of broadly protective vaccines based on influenza virus proteins that are shared by multiple strains.

NIAID has been very successful in the past with ground-breaking vaccine research, including scientific advances that led to the development of hepatitis B, *Haemophilus influenzae b*, pneumococcal pneumonia, acellular pertussis, and live-attenuated intranasal influenza vaccines. I am confident that the approaches that we are currently pursuing with influenza will lead to a next-generation vaccine that improves upon the current egg-based technology.

In addition to developing influenza vaccine candidates, NIAID has developed an extensive capacity for clinically evaluating these products. For example, NIAID's Vaccine and Treatment Evaluation Units (VTEUs) comprise a network of university research hospitals across the United States that conduct clinical trials to test candidate vaccines for infectious diseases. These units can be accessed by both academic and industrial vaccine developers to evaluate the safety, immunogenicity, and ultimately, the efficacy of candidate vaccines.

Therapeutics

Antiviral medications are an important counterpart to vaccines, both to treat infection after it occurs and to prevent illness after exposure; four drugs are

currently available for the treatment of influenza, three of which are also licensed for prevention. NIAID actively supports identification of new anti-influenza drugs through the screening of new drug candidates in both cell culture and in animals. In the past year, seven promising candidates have been identified. Efforts to design drugs that precisely target viral proteins and inhibit their functions also are under way. In addition, NIAID is developing novel broad-spectrum therapeutics against many influenza virus strains; some of these target viral entry into human cells, while others specifically attack and degrade the viral genome.

Pandemic Influenza

Although the impact of influenza on morbidity and mortality in a normal epidemic year is substantial, much more serious influenza pandemics also can occur. As influenza viruses spread, they continuously evolve and accumulate small changes in their outer coat proteins, a process called “antigenic drift.” This occurrence allows the virus to at least partially escape the human immune responses primed by vaccination or exposure to earlier versions of circulating influenza viruses. Influenza viruses can also jump species directly from certain animals such as chickens to human as well as swap genes with influenza viruses that infect birds, chickens, pigs, or other animals; the latter process is referred to as “reassortment”. When such reassortment events occur, the result is the replacement of one or more of the outer coat proteins of the human virus with that of the animal virus, or an “antigenic shift.” If the virus that has jumped species or the new reassorted virus evolves to be efficiently transmitted between

people, a deadly influenza pandemic can result. As the population acquires immunity to the new strain over the next several years, the pandemic strain fades into the routine background of circulating viruses.

Three influenza pandemics occurred in the 20th century, in 1918, 1957, and 1968. The pandemic that occurred in 1918-1919 was the most severe, killing 20-40 million people worldwide, including more than half a million individuals in the United States. The pandemics that began in 1957 and 1968 killed approximately 2 million and 700,000 people worldwide, respectively.

One of the first internal committees Secretary Thompson created when he came to HHS was on pandemic flu. And last August, the Secretary unveiled the Department's draft Pandemic Influenza Response and Preparedness Plan. This plan outlines a coordinated national strategy to prepare for and respond to an influenza pandemic.

NIAID conducts research to understand the viral biology and epidemiology that underpinned past pandemics, and funds an extensive surveillance network in Asia to detect the emergence of influenza viruses with pandemic potential. In addition, the draft U.S. Pandemic Influenza Preparedness and Response Plan describes specific roles for NIAID should a pandemic occur. Foremost among these is to help develop and produce an effective vaccine as rapidly as possible. Specifically, NIAID will help to characterize the newly emerging influenza strain,

isolate candidate vaccine seed viruses, develop investigational batches of candidate vaccines, and produce and distribute research reagents for use by vaccine researchers in academic and pharmaceutical industry laboratories. NIAID will also work with industry to produce and clinically test pandemic influenza vaccines at different doses and in different populations in our vaccine clinical trials sites, and will coordinate closely with CDC, FDA, and WHO to provide a safe and effective vaccine to the public as quickly as possible.

In recent years, several avian influenza virus strains that can infect humans have emerged. In 1999 and 2003, an H9N2 influenza strain caused illness in three people in Hong Kong. The H5N1 "bird flu" virus, first detected in humans in 1997, infected at least 44 people and killed 32 in 2004, and has spread widely among wild and domestic birds. There has been at least one documented case of human to human spread of an H5N1 virus. NIAID already has taken several steps to develop vaccines against both of these potential pandemic strains. To address the H9N2 threat, NIAID contracted with Chiron Corporation to produce investigational batches of an inactivated vaccine, which will be evaluated clinically by NIAID early next year. For H5N1, Aventis-Pasteur, Inc. and Chiron are both producing investigational lots of inactivated H5N1 vaccine preparations; additionally, DHHS has contracted with Aventis to produce up to 2 million doses to be stockpiled for emergency use, if needed, to vaccinate health workers, researchers, and, if indicated, the public in affected areas.

Development and evaluation of a combination antiviral regimen against these potential pandemic influenza strains are also now under way.

Transforming the Flu Vaccine Marketplace for 21st Century

President Bush has invested more in research, development and acquisition of flu vaccines and medicines than any President in our nation's history in an effort to revitalize a deteriorated flu vaccine marketplace and better protect the American people.

Conclusion

Given the disruption of the influenza vaccine supply that we experienced this year, and the inherent difficulties associated with the current manufacturing technology, it is clear that we must move toward next-generation influenza vaccines with all deliberate speed. NIAID's role in influenza vaccine development is to carry out the research upon which these new vaccines will be based, and to forge productive partnerships with private sector pharmaceutical and biotechnology companies to speed development and clinical evaluation of promising candidates.

In closing, Mr. Chairman, I would like to take a moment to remember John R. La Montagne, Ph.D., deputy director of NIAID, who died suddenly on November 2 while traveling to a meeting of the World Health Organization in Mexico City. Throughout his almost 30-year career at NIH, John's leadership

and commitment to improving global health, particularly in the arena of influenza vaccine research, were remarkable. His generosity, wit, even-handedness and kindness made him a friend to all who knew him. Personally, he was a dear friend and one of the finest people I have ever known. He will be sorely missed.

I would be pleased to answer any questions you may have.